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THE BIOCHEMISTRY OF PSORIASIS.

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Psoriasis, I should judge, has been more investigated than any other skin disease, with findings that are often difficult to relate one to another. In this paper I am attempting to summarize the literature available to me on biochemical investigations in this disease and to draw conclusions as to which lines are likely to prove fruitful in future. For convenience, I shall deal with matters under the headings lipids, proteins, carbohydrates, minerals and miscellaneous.

Lipids.

Histochemical demonstration of excess lipids in the psoriatic lesion was observed by von Kerckhoff (1929) and Grütz (1938). These findings were confirmed by Steigleder (1952) and Dogliotti (1953). However, the findings were not specific for psoriasis, since Dogliotti found similar changes in seborrhoeic dermatitis. Braun-Falco (1958) stated that lipids, such as phospholipids and unsaturated lipids normally occurring in the transitional zone underneath the stratum corneum, extended throughout the parakeratotic layer. He attributed this to more rapid keratinization in psoriasis, allowing less time for the normal disappearance of these lipids.

By conventional chemical methods, Incedayi and Ottenstein (1940) found an increase in the cholesterol content both of sound psoriatic skin and of psoriatic lesions. Bürger (1938) and Cornish, Block and Lea (1959) found an increase in the lipids of psoriatic scales, the constituents of which were mostly neutral fats. The cholesterol present was mostly free. Although total skin cholesterol was raised, the cholesterol content of skin washings was unaffected (Marchionini, Manz and Huss, 1938).

Patterson and Griesemer (1959) have studied the uptake of radioactive carbon

into various fractions of the lipids of psoriatic lesions compared with adjacent sound skin. The activity of squalene from the lesions was only about 5% and of fatty acids about 25% of that of surrounding normal skin. By contrast, the activity of the sterol fractions was slightly increased in the lesions. Other experiments on normal skin showed that squalene was almost entirely a dermal product while sterols were almost entirely epidermal products. Thus it seems very possible that many of these findings were due to different relative proportions of dermis and epidermis in the samples of normal and diseased skin investigated.

Rothman (1950) found that the skin surface fat of psoriatics showed the following changes : a decreased acid number, a decreased iodine number and a decrease in the proportion of cholesterol esterified. One may infer a diminution of free acids and of unsaturated fats.

Blood lipids have been extensively investigated in psoriasis. Many findings are recorded for serum cholesterol and have ranged from values averaging 50% above normal (Radl, Kraus and Tousek, 1957) to 10% below (Rosen, Rosenfeld and Krasnow, 1937). On the whole more authors have reported increases (Grütz and Bürger, 1933 ; Bürger, 1938 ; Madden, 1939a ; Lévy-Franckel and Bréant, 1948 ; Radl, Kraus and Tousek, 1957 ; Shapiro, Knox and Grundy, 1958) than no change or decreases in serum cholesterol (Rosen, Rosenfeld and Krasnow, 1937; Incedayi and Ottenstein, 1940 ; Dodds, MacCormac and Robertson, 1942 ; Castro-Mendoza and Orbaneja, 1946. Nevertheless, the only fact that I am confident about in this connection is that the more widespread the disease, the lower is the serum cholesterol (Neumark, 1931 ; Tickner and Mier, 1960).

Total lipids of serum were claimed to be raised by Bürger (1938) and by Radl, Kraus and Tousek (1957). On the other hand they were found to be normal by Castro-Mendoza and Orbaneja (1946). Marked decreases in conjugated unsaturated fatty acids of the serum were reported by Musger, Zirm and Schauenstein (1952). Abnormal cholesterol tolerance tests in psoriasis were affirmed by Grütz and Bürger (1933) and denied by Rosen, Rosenfeld and Krasnow (1937), Le Winn and Zugerman (1941), and Dodds, MacCormac and Robertson (1942). Levi, Meneghini and Pozzo (1953) found chylomicrons cleared unusually slowly from psoriatics following a fatty meal while abnormalities of both serum phospholipid and cholesterol levels were found in psoriatics following administration of lecithin (Melczar and Bodsay, 1958) ; Hnat, Janke and Kappelmacher (1954) found no change in blood cholesterol-esterase in the serum of psoriatics while Klemm and Grasneiner (1954) also reported serum lipase in psoriatics to be normal or slightly raised. Thus the apparently important lipid findings may be summarized : there is an excess of lipid in the lesions of psoriatics which is doubtfully associated with a raised serum cholesterol level. The latter certainly falls as the extent of diseased skin increases.

Protein Metabolism.

Perhaps the best attested phenomenon with regard to protein metabolism in psoriasis is the prevalence of –SH groups. These have been demonstrated in excess in the parakeratotic horny layer histochemically (Moncorps, 1929 ; Percival and Stewart, 1930 ; Sannicandro, 1932 ; Zingsheim, 1952, 1954 ; Steigleder, 1956 ; Braun-Falco, 1957.) The phenomenon has also been shown by conventional chemical means in scales by Van Scott and Flesch (1954) and Magnus (1956). The former authors stated that the sulphydryl groups of psoriatic scale were bound exclusively to soluble proteins. Magnus showed that the increased –SH was not peculiar to psoriasis and that these groups diminished on boiling.

Total sulphur of scales is said to be the same as that of scales following ultraviolet irradiation (Cornish, Block and Lea, 1959) although earlier workers claimed that there was a rise in total sulphur in psoriatic skin in both lesions and sound skin (Klauder and Brown, 1936). A different aspect of sulphur metabolism was dealt with by Lipnik and Levy (1959). Methionine labelled with radioactive sulphur was administered to psoriatics and to normal patients. The epidermal radioactivity was measured at intervals. Control skins reached a peak of radio-activity after three hours and were clear of it in four days. The sound skin of psoriatics behaved similarly to normal skin except that the radioactivity persisted slightly longer. By contrast, the radioactivity in psoriatic lesions did not reach a peak, which was much higher than normal, until after four days. The radioactivity was still high at the conclusion of the experiment seven days after the methionine was given. Thus it would appear that the methionine is fairly rapidly metabolized by normal epithelium whereas it is more firmly attached in the psoriatic lesion. Of course it must be remembered that the evidence presented does not say anything about the nature of the sulphur present—it might still be present as methionine, as cystine or cysteine or even perhaps not as part of an amino acid at all.

Another anomaly of protein metabolism was reported by Schmidli and Paschoud (1955). They found that amino acids were unaffected but that water soluble polypeptides were very markedly reduced to 40% of the normal value in psoriatic lesions. The unaffected skin of psoriatics was normal in this respect. The presence or absence of scales on the lesion did not materially affect the result. In further work (Paschoud, Keller and Schmidli, 1956) characterized by Shelley and Arthur (1958) as " dermatologic research in its finest flowering " and regarded by Flesch and Esoda (1958) as possibly describing an artefact, it was shown that alanyl-glycine, glycyl-glycine and leucyl-glycine dipeptidase activities of homogenates of affected (but not unaffected) psoriatic skin was significantly reduced. The last named enzyme, sometimes termed leucine amino-peptidase, is a proteolytic enzyme. Since it was shown

that the diminished activity of these enzymes was due to an inhibitory factor present in scales, I feel that Flesch and Esoda's explanation, namely, that because of the way specimens were taken, less epithelium was included in the specimens from psoriatic lesions compared with those from normal skin, is unlikely to be a completely satisfactory one. The finding of decreased water soluble amino nitrogen has been confirmed by Flesch and Esoda (1957). Various volatile amines, nitrogenous compounds probably derived from bacterial breakdown of amino acids, have been found in watery extracts of psoriatic scales by Zorn (1954).

Some investigators have set out to find if the psoriatic scales show any qualitative changes with regard to the amino-acid composition of the proteins. Hahnel (1957) found that there were no qualitative differences between end amino groups of normal horn and psoriatic scales, but changes in reactivity did exist and he thought this might be due to quantitative changes in these substances. Flesch (1958), has shown that there is a relative increase in arginine in psoriatic stratum corneum. Zahnd and Citron (1960) also reported a relative increase of arginine and lysine in hydrolysates of psoriatic scales accompanied by a relative decrease of the sulphur containing amino acids cystine and cysteine. On the other hand Cornish, Block and Lea (1959) said that the amino-acid composition of psoriatic scales did not differ from scales obtained from normal people by desquamation following ultra-violet irradiation. The subject seems to me to merit further examination. Both arginine and lysine are basic amino acids with residues in proteins which are positively charged at physiological pH. The very remarkable effects of a change of charge in one residue is shown by the effect of substituting for one single amino-acid residue—the negatively charged glutamic acid—in haemoglobin, the uncharged residue valine. This substitution gives rise to haemoglobin S—the haemoglobin responsible for sickle cell anaemia. It needs no emphasis on my part to see how a very slight change in protein structure can give rise to very far reaching effects. However, the possibility of such changes being present in psoriasis must wait until the essential but difficult task of determining the sequence of amino acids in normal and abnormal keratins has been carried out.

Normally one thinks of stratum corneum as an inert tissue and in general this is true. However, if there is an enzyme in epidermis which remains stable even on drying at room temperature, then it is apparent that as drying proceeds the apparent concentration of the enzyme will increase considerably. Since the enzyme arginase occurs in epidermis (Mardashev and Semina, 1948 ; Van Scott, 1948) it is apparent that if it is a reasonably stable enzyme then it will occur in stratum corneum in enhanced concentration. This has in fact been observed (Rothberg and Van Scott, 1958), but the matter is a little more complicated since scales of psoriasis were richer in arginase than normal stratum corneum while stratum corneum from the skin of the trunk was less rich than

normal plantar callus, the ratio of activities psoriatic scale : plantar callus : normal stratum corneum being 10 : 6 : 1. Apparently also there is something in normal epidermis which inhibits arginase activity in psoriatic scale, but the nature of this inhibitor is unknown.

Arginase is an essential component of the urea synthesizing mechanism of the body so this observation of Rothberg and Van Scott has to be reconciled with that of Rothman (1950), who found that the ratio urea nitrogen : total nitrogen was decreased in water wipings of skin. Since at least the potential production of urea is increased in psoriatic scales it seems probable that Rothman's findings are likely to be due to an increase in water soluble nitrogen other than urea.

The psoriatic horny layer contains appreciable quantities of proteins extractable by water and coagulable on heating (Flesch and Esoda, 1958). Much smaller quantities are obtained from normal callus. Roe (1958) has extracted the proteins from borate buffer dispersates of psoriatic scales. She was able to separate three protein fractions. Protein A was one of isoelectric point at pH 5·5 and was shown by electron microscopy to form fibrils of 65 Å diameter which tended to join up side by side with other fibrils to form bundles of about 200 Å diameter. Its properties caused Roe to consider it to be identical with tonofibrin, a keratin precursor extractable from normal epidermis. It is said not to possess sulphydryl groups (Flesch and Kun, 1950). Protein B was a globular protein containing sulphydryl groups. Its behaviour with appropriate dyes and direct analysis showed it to be a mucoprotein said to contain N-acetyl glucosamine and sulphate. Protein C could be demonstrated to contain nucleotides and pentose. It gave a positive Feulgen reaction and was therefore thought to be a nucleoprotein. Protein A therefore was concluded to be a normal intermediate of keratinization which had accumulated in psoriatic scales in the absence of proper keratinization. It was present in normal epidermis but not in normal callus. Protein B occurred in traces in normal epidermis, not at all in normal callus. It was present in the scales of non-psoriatic exfoliative dermatitis, but there in contrast to psoriasis it was entirely extracellular. Roe felt that possibly the presence of this protein might inhibit the maturation of keratin. Protein C was believed to persist in scales as remnants of the parakeratotic cell.

Some of the most interesting work in this connection has been published by Swanbeck (1959). He has investigated the macromolecular organization of epidermal keratin by x-ray diffraction. As a result of his findings, and the mathematical analysis of them, Swanbeck says that keratinization occurs in the following fashion. In the lower layers of the epidermis, filaments of protein are synthesized with a diameter of 100 Å. Other cellular elements decompose, but these filaments join side by side (cf. the behaviour *in vitro* of Roe's protein A) in bundles of 5–10 with a diameter of 250 Å. These bundles are coated

with a layer of lipids 80 Å thick. In psoriasis, the aggregation of filaments into bundles does not occur so that protein filaments not exceeding 100 Å thick occur in the stratum corneum. We have therefore to explain why there should be this lack of aggregation. It is frequently assumed that this is associated with a failure of –SH groups from one protein chain to unite with those of another. This may be true. Certainly Swanbeck made the reasonable assumption that lateral aggregation occurred by disulphide formation while –SH groups occurred only on the free surface. Using this hypothesis, simple calculation from published data on –SH and total S of the stratum corneum in various skin conditions leads to results in close concordance with those found by x-ray diffraction.

However it seems reasonable to equate these protein fibrils with protein A of Roe, who stated that this contained no –SH groups and in any case aggregated spontaneously *in vitro*. Thus it seems reasonable to suppose that some factor is present in psoriatic scale which inhibits aggregation. Possibly this is protein B, as Roe hinted. One wonders to what degree the persistence of protein B is related to the lowered leucine amino-peptidase mentioned earlier. If the smaller fibrils of psoriasis are also covered with grease as the normal bundles are, about three times as much lipid would be present in psoriasis as in normal epidermis. Although an increase in lipid has been described in psoriatic scale, it is not a threefold increase. Could proteins uncovered by lipid retain enzymic activity and thus account for the raised arginase observed ?

Obviously the failure of aggregation of the fibrils and the persistence of the mucoprotein B are of the utmost importance but these facts now require to be explained. Still it seems likely to me that it is in this field that major advances in the problem of psoriasis will be made.

Serum Proteins.

Serum proteins have been estimated many times with conflicting results (Lever, Schultz and Hurley, 1951 ; Ricciardi, 1952 ; Bolgert, Blamoutier and Moret, 1954 ; Norman, 1954 ; Schneider, 1955 ; Radl, Kraus and Tousek, 1957 ; Lea, Cornish and Block, 1958 ; Kalz *et al.*, 1958 ; Tickner and Mier, 1960). I confess to a degree of prejudice in favour of our own findings since ours is the largest published group and a statistical analysis was made of the results. We found a significant fall in mean values of total protein and albumin and a significant rise in means of α_2- and β-globulins. As the disease becomes more and more widespread, the abnormalities follow the stereotyped pattern of diminishing total protein and albumin and increasing globulin fractions with the exception of the β-globulin fraction which like the serum cholesterol drops as the disease becomes more widespread. But while these changes occur between mean values of large groups, individual protein values in psoriasis usually show no change or slight change from normal.

Lipoproteins have been studied both by paper electrophoresis and by use of the ultra-centrifuge. α-lipoproteins were found to be lowered and β-lipoproteins to be raised by Meneghini, Levi and Pozzo (1953) and these findings were confirmed by Radl, Kraus and Tousek (1957). However, Huriez, Desmons and Agache (1957) found rather less clear-cut results. Of their series of 26 cases 46% had a normal, 35% a raised and 19% a lowered β-lipoprotein. As regards the α-lipoprotein, this was most commonly raised in recent psoriasis, never in chronic disease. Lever (1953) found no change in either α- or β-lipoproteins in psoriasis.

Flotation values show a wider spread than usual (Pozzo, Levi, Meneghini and Prati, 1953). Shapiro, Knox and Grundy (1958) found low-density and very low-density lipoproteins (high fat content) to be low in psoriatics. Recently (1960) the same authors have shown that if changes are induced in the lipoproteins in psoriasis, the disease remains unaffected.

Serum glycoproteins have been found to be raised by Lever (1953), Weber, Braun-Falco and Thaesler (1954) and Burbach (1955). The latter, with the largest series, stated that the rise was confined to severe cases of the disease.

Whatever the changes in serum proteins in psoriasis, it would appear likely that they are secondary to the disease rather than the other way round. Still, these changes remind us that the skin is firmly fixed to the rest of the body.

Carbohydrate Metabolism and Related Topics.

Carbohydrate metabolism has been extensively reviewed by Ribuffo (1957) and I quote here his main conclusions. There is, he said, a raised aerobic and anaerobic glycolysis in the psoriatic lesion ; an increase over normal values of the sugar content of the sound skin of psoriatics ; and abnormalities of the levels of inorganic phosphate and alkaline phosphatase of blood in psoriatics, following administration of glucose.

An excess of glycogen occurs in the epidermis of psoriatics (for review see Braun-Falco, 1958) but this, although characteristic, is non-specific. Pentoses, presumably derived from the break-down of nucleic acids, have been reported in increased quantity by Buckup and Szakall (1957) and Flesch and Esoda (1958).

Szakall and Weber (1959) said that in watery extracts of psoriatic scales, a considerable amount of inorganic phosphate and some organic phosphate, hydrolysable only with difficulty (i.e. probably simple phosphate esters) could be demonstrated. Only organic phosphorus could be demonstrated in the stratum corneum of sound skin. Editorial comment on this paper sought to relate these findings to a putative difficulty of phosphorylation in psoriatic skin.

Here I wish to quote unpublished work carried out in my laboratory by Mier (1959) and Mier and McCabe (1960). Psoriatic skin incubated *in vitro* in

a Krebs-Ringer medium containing radioactive phosphorus showed a higher ratio of organic acid soluble radioactive phosphorus to inorganic radioactive phosphorus, than normal skin incubated under the same conditions. This implies either a higher content of organic acid soluble phosphorus in psoriatic skin or a more rapid incorporation of inorganic phosphate into the organic fraction.

Two-way chromatography followed by radio-autography of acid soluble extracts of skin, incubated with radioactive phosphorus, by the method of Brooks, Lawrence and Ricketts (1959) show many phosphorus containing compounds both in normal and abnormal skins and by this technique, in contrast to the findings of Szakall and Weber, inorganic phosphorus can always be detected. Unfortunately, owing to the different rates at which these compounds reach equilibrium with radioactive inorganic phosphate, it is impossible to use the method in its present form to give a reliable measurement of the individual compounds found. Also the amounts of these materials in skin are so small as not to be measurable by any other method so far devised if one uses practicable biopsy specimens.

It has also been found that if the highly specific glucose oxidase method of estimating glucose is used, very small quantities of this substance occur in either normal or abnormal skin. This therefore makes one a little hesistant in attempting to assess the significance of the finding of Monacelli and Ribuffo (1952) that the skin sugar in psoriasis is raised.

Some of the other findings of Mier and McCabe are set out in Table I.

TABLE I.—(*Mier and McCabe*, 1960). *Ratio of Content of Some Components of Human Skin Relative to Content of Deoxyribonucleic Acid.*

Component.	Normal.	Psoriasis.	Eczema.
Acid soluble phosphorus	1·0	1·29	1·46
Lipid phosphorus	1·21	1·0	1·05
Ribonucleic acid	0·46	1·02	0·63
Lactic dehydrogenase	3·8	3·9	4·0
Hexokinase	0·83	0·69	1·3
Deoxyribonucleic acid	1·0	1·0	1·0

In this table the ratio of various components to deoxyribonucleic acid is set out. By this means one overcomes differences merely due to different numbers of presumably viable cells. For instance the mean values found for lactic dehydrogenase are 9 units and 23 units per gram wet weight in normal and psoriatic skin respectively, but since deoxyribonucleic acid levels vary from 2·4 micromoles DNA phosphorus per gram in normal skin to 5·8 micromoles DNA phosphorus per gram in psoriatic skin, one can see that lactic dehydrogenase per cell is unaffected in psoriasis being 3·8 units/micromole DNA phosphorus in normal skin and 3·9 units/micromole DNA phosphorus in psoriatic skin. Perusal of the table shows that by far the most marked effect

in psoriasis is the rise in ribonucleic acid. This bears out the histochemical finding of Steigleder (1955) that cytoplasmic ribonucleic acid is elevated in psoriatic epidermis.

Mineral Metabolism.

Schamberg and Brown (1930) found normal values for serum calcium, magnesium, potassium and phosphate in psoriatics. Reinberg *et al.* (1958) also found normal values for plasma potassium, sodium, chloride and bicarbonate. However, statistical analysis showed that as psoriatics improved, plasma potassium and chloride diminished while the bicarbonate increased. Thus clinical improvement is associated with a loss of potassium from the extracellular fluid and one must assume the potassium is excreted or more probably moves into cells. The latter possibility would appear to be discounted since Dörffel (1930) and Reinberg *et al.* (1958) showed that psoriatic lesions were in fact richer in potassium per unit weight than normal skin: 36·6 and 19·2 mEq./Kg. fresh skin respectively. Using my laboratory's findings for the DNA of psoriatic and normal skin, we find potassium to be present to the extent of 8 Eq./mole DNA phosphorus in normal skin and 6·31 Eq./mole DNA phosphorus in psoriatic skin. Thus the undoubtedly increased potassium of psoriatic skin did not in fact increase *pari passu* with the cellularity and one would expect that serum potassium would decrease as the lesion healed.

Hodgson (1960) in my laboratory has estimated the sodium and potassium of normal and diseased epidermis. The former is unaffected by disease but the latter shows changes summarized in Table II.

Table II.—*Potassium Content of Normal and Abnormal Epidermis (mEq./Kg. Wet Weight).*

Condition.	Potassium concentration.
Normal	34·9 ± 1·21
Psoriasis, acute lesion	102·0 ± 15·2
,, subacute lesion	73·1 ± 9·3
Eczema	80·6 ± 11·2
Chronic lichen simplex	81·8 ± 7·3

The raised potassium values seen in psoriasis are non-specific although more marked than in eczema and chronic lichen simplex, which also show rises. My initial hypothesis was that these disturbances merely mirrored the increase in cells but further work by Hodgson on epidermal DNA leads to the inference that in acute psoriasis at least there is an actual increase of potassium/mole DNA phosphorus in contrast to our calculations for whole skin cited above. If this increase is truly due to an increase of potassium concentration in the individual acanthotic cell and not due to an increase in cells relatively rich in potassium, some of this increase might go to preserve electrical neutrality with the increased RNA phosphorus found in psoriasis.

Miscellaneous.

Table III records a hodge-podge of observations in psoriasis which cannot readily be placed in any logical pattern at the moment and discussion of which would lengthen this paper beyond all reasonable limits. I content myself with pointing out that Reiss's finding on vitamin C depletion has been confirmed in this laboratory (Tickner and Basit, 1960).

Table III.—*Miscellaneous Findings in Psoriasis.*

Author.	Observation.
Konopik (1955)	High cysteine content in sweat.
Hoffman, Schneider and Quamo (1950)	Serum vitamin A raised in female psoriatics.
Jensen (1948)	Biotin excretion reduced.
Magnusson and Jensen (1952)	Urinary 17-ketosteroids low in 15% normal in 85%.
Csermely (1954)	Urinary 17-ketosteroids low in 50%.
Boncinelli and Trimigliozzi (1953)	Adrenal function normal.
Reiss (1949)	48% low urinary 17 keto-steroids. 36% flat glucose tolerance curve. 88% vitamin C depletion. 20% increased serum K^+. 12% decreased serum Na^+. 25% high blood cholesterol.
Caceialanza and Levi (1951)	40% of males, 0% ,, females } low urinary 17 ketosteroids. 15% of males, 11% ,, females } high ,, 17 ,,
Heim and Ruete (1946)	Normal serum cholinesterase.
Snider, Gottschalk and Rothman (1949)	High choline content of scales.
Madden and Karon (1953)	Faecal fat low in 33%. ,, N ,, ,, 27%. Serum amylase low in 13%.
Anwander and Janke (1954)	Amylase, trypsin and bilirubin of pancreatic juices rather low.
Gaul and Staud (1934)	Abnormal retention of nickel by psoriatic skin.

Table IV shows the finding of serum uric acid in psoriatics made by various authors. I am sceptical about any appreciable disturbance of purine metabolism in this disease.

Table IV.—*Serum Uric Acid in Psoriasis.*

Author.	Finding.
Herrman (1930)	Non-psoriatics 5% over 5 mg%. Psoriatics 31% ,, 5 ,, Psoriatic arthritics 78% ,, 5 ,,
Madden (1939b)	10% above 4 mg%.
Steinberg *et al.* (1951)	48% of males, 27% of females show raised values.
Lobitz and Brunsting (1954)	15% of psoriatics show raised values.
Lea, Curtis and Bernstein (1959)	No abnormalities.
Tickner and Mier (1960)	21% over 5 mg%. 3·5% over 6·5 mg%.

Comment.

Allowing oneself a paragraph of speculation from the aforementioned facts, I personally would adopt the following hypothesis.

(i) The psoriatic lesion results from a failure of union of tonofibrin fibrils (Roe's protein A).

(ii) This failure occurs as a result of the presence in the lesion of a substance present in abnormally large quantity.

(iii) This substance is probably anionic at physiological pH and occurs as the result of some metabolic block.

(iv) This block will be found only by systematic research into enzymes and components of normal and abnormal skin.

Finally, it is distressing to note the small part played by British investigators in this field. Unfortunately I cannot see much improvement in this connection until more clinical dermatologists are trained in biochemistry and more biochemists in dermatology or at least in dermatological histopathology. For the biochemist without knowledge of dermatology is myopic but the investigative dermatologist without knowledge of biochemistry is impotent and his endeavours will be unfruitful.

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BLOOD LIPIDS IN PSORIASIS.

The Effects of " Lipostabil ".

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Dietary deficiency of certain polyunsaturated fatty acids results in skin changes in rats not unlike those seen in human psoriasis. Accordingly an attempt was made to employ them in the treatment of the latter.

Fatty acids may be administered therapeutically either as emulsions or in combination as in phospholipids. When the latter are employed, refined extraction methods can result in a preparation containing almost exclusively those acids important in the nutrition of rat dermis. These are the so-called essential fatty acids or Vitamin F acids, linoleic, linolenic and arachidonic. A much lower dose of total fatty acids can therefore be employed and the preparation can be administered as capsules rather than as an unpalatable and to some subjects unacceptable emulsion. The preparation used was that marketed by Nattermann of Cologne as " Lipostabil ". In the original formula there are a number of non-fatty substances with other therapeutic effects and these were omitted from the capsules we have administered.

Investigation.

Two groups of six women with psoriasis were studied : one was treated with the active preparation and the other with a placebo (Table I). Each active capsule contained 320 mg. of soya bean extract and 0·6 mg. of pyridoxine, with 0·1 mg. α-tocopherol as an antioxidant. The placebo capsule contained lactose and α-tocopherol. Various doses were given but most subjects received six capsules a day. Cases were allotted to treatment and placebo groups on a random series by the pharmacist and neither physician nor pathologist knew the distribution before the trial was completed. The serum content of the substances shown in Table II was estimated before treatment after a twelve hour fast. The mean value of and

Table I.—*The Clinical Characteristics of the Groups.*

	Subjects	
	Treated	Control
Number	6	6
Mean age (years)	32	22·5
Number taking adequate doses for 3 months or more	6	4
Clinical change :		
Improvement	0	2
No change	6	2
Worse	0	0
Sex	Female	Female

standard deviation (s.d.) for each substance in each group were calculated and no significant differences between them were discovered. Accordingly, Table II shows the mean value and s.d. for each of these substances in the whole series of twelve patients. Although the differences between the groups in no case reached the conventional limits of significance ($P < 0.05$), the control group had a mean age nearly ten years less than the other and the lipid levels in it were rather lower (see also Table III).

TABLE II.—*Blood Lipids in Cases of Psoriasis Before Treatment and After a 12 Hour Fast.*

	Mean Values	Standard deviation
Whole blood cholesterol mg./100 ml.	198·3	55·9
Total fatty acids in mEq/l. (Stern and Shapiro, 1953)	9·54	2·21
Phospholipid in mg./100 ml.	195·2	64·3
Total lipids mg./100 ml.	679·8	108·8
Lipoprotein :		
$\frac{\text{alpha}}{\text{beta}}$ ratio	0·38	0·265
$\frac{\text{pre-beta}}{\text{beta + pre-beta}}$ ratio	0·08	0·122
$\frac{\text{alpha}}{\text{pre-beta}}$ ratio	32·8	–
Beta lipoprotein in units/100 ml. (after Burston and Samaille 1956)	5·62	2·49
Pre-beta lipid (same units as above)	0·60	0·648
Pre-beta lipid in Smith (1957) units	0·8	0·84
Gamma globulin in Kunkel units/ml.	5·40	1·92
Transaminase (S.G.O.T.) in Sigma Frankel units/ml.	12·2	3·36
Accelerated clotting time in secs (average normal control 16 secs.)	17·3	5·24
E.S.R. mm./hr. (Wintrobe)	15·0	13·2

TABLE III.—*Changes in Blood Lipids During Three Months' Observation.*

	Treated Group		Control Group	
	Initial mean value	Mean value after 3 months	Initial mean value	Mean value after 3 months
Whole blood cholesterol in mg./100 ml.	221	221	176	249
Total fatty acids in mEq/l. (Stern and Shapiro, 1953)	9·6	8·3	9·5	12·5
Phospholipid in mg./100 ml.	215	182	175	181
Total lipids in mg./100 ml.	724	672	636	792
Lipoprotein :				
$\frac{\text{alpha}}{\text{beta}}$ ratio	0·38	0·27	0·38	0·6
$\frac{\text{pre-beta}}{\text{beta + pre-beta}}$ ratio	0·08	0·13	0·08	0·16
$\frac{\text{alpha}}{\text{pre-beta}}$ ratio	21·9	4·7	43·8	10·8
Beta lipoprotein in units/100 ml. (after Burston and Samaille, 1956)	6·3	7·1	5·0	6·3
Pre-beta lipid (same units as above)	0·55	0·87	0·65	1·5
Pre-beta lipid in Smith (1957) units	0·8	0·7	0·5	0·6
Gamma globulin in Kunkel units/ml.	5·2	5·9	5·8	8·5
Transaminase (S.G.O.T.) in Sigma Frankel units/ml.	15	13	10	15
Accelerated clotting time in secs. (average normal control 16 secs.)	17	17	19	17
E.S.R. in mm./hr. (Wintrobe)	17	12	13	9

Cases were seen fortnightly at first and later monthly. For the first three months of treatment, local applications were not used. Progress was recorded regularly and a final assessment made at a single session when all the cases were compared. Table I shows that the preparation had no effect on the clinical condition.

Table III shows the mean values of fasting levels of serum lipids, which were estimated at each attendance, in treated and placebo groups and before and after treatment. There are no changes of any magnitude in the blood chemistry of the treated subjects and such changes as are seen in the control group (which is smaller since two patients defaulted) are not significant.

Discussion.

The mean values of all these blood lipids approximate closely to the accepted normals for women of this age.

The normal level of whole blood cholesterol should be about 200 mg. % (Schettler and Brückel, 1958, and *Lancet* editorial, 1957), the mean observed value being 198 mg.

The mean fatty acid level of 9·5 mEq/l. is similar to that of 9·2 mEq/l. of Bauer and Hirsch (1949) for fasting subjects and to the mean of 11·6 mEq/l. of Morgan and Kingsbury (1959) although it does differ significantly from a personal series of 50 non-fasting female blood donors (12·0 mEq/l. ; standard error of differences : 0·61).

The beta lipoprotein value assessed by heparin flocculation appears to be rather low, the normal mean for 105 blood donors being 9·6 units. The difference is significant (standard error of difference 0·55 units) but again the blood donors were not fasting. The other values for single substances are all within the established normal ranges. The accelerated clotting times did not differ significantly from those of normal controls.

Directly comparable normal values for the ratios are not readily available. A proportion of three parts of beta lipoprotein to one of the alpha fraction is recognised as normal. Figures for pre-beta lipid have not been published and it is widely held that this substance is very difficult to quantitate. All three methods for measuring it suggest that a proportion of about one tenth of total beta lipoprotein is composed of pre-beta lipids. This correspondence of a ratio of one tenth representing one Smith (1957) unit agrees with many other duplicate analyses made here and personal experience suggests that both values are normal. Alpha/pre-beta lipid ratios do not appear to have been used previously but this figure is also an approximately normal value. In deriving it the ratio was conventionally held to be 100 if no-pre-beta lipid was detected.

Tickner and Mier (1960) reported on the blood cholesterol level in 86 psoriatics of both sexes and listed a number of authorities who state it is raised and one who claims it is lowered. They concluded that it is moderately elevated in about a third of severely affected subjects but none of ours was so affected.

There are numerous reports on the effect of this extract of phospholipids on the abnormal blood fats of arteriosclerotic subjects (see e.g. Schettler and Brückel, 1958) but none of them describe prolonged administration to subjects such as these whose blood fats are initially normal. In this series, no changes were induced although the treatment may have had some effect in stabilizing the normal pattern, since the controls appeared to vary more than the test subjects.

Kageyama and Morita (1959) had some clinical success in 2 out of 4 subjects and Dr. H. R. Vickers saw some improvement in 9 out of 14 subjects after one month's treatment (Alcock, 1959). Neither, however, reported the results of prolonged treatment or used controls. Two of the Japanese subjects showed some improvement in the levels of some of the blood lipids, but this was not statistically significant. Our results after adequate dosage for at least 3 months and in some cases as long as 7 months, were most disappointing.

Summary.

Twelve female subjects with psoriasis were randomly allotted to treatment and placebo groups for a trial of treatment with " Lipostabil ", a preparation containing unsaturated fatty acids. The levels of ten of the common fractions of the blood lipids and four other parameters were determined serially throughout treatment.

There was no clinical response to the drug and the levels of blood lipids, which were initially normal, did not change during or after this treatment.

Some of the expense of this investigation, which is part of a large scale clinical trial, was defrayed by Aspro-Nicholas Ltd., of Slough, Bucks. who market 'Lipostabil' in this country. The trial would be impossible without the willing co-operation of our Chief Pharmacist, Mr. J. Parker.

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ORAL STEROID THERAPY IN PSORIASIS VULGARIS.

A Comparison of Triamcinolone, Methyl Prednisolone and Dexamethasone.

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At the International Congress of Dermatology in 1935, Kissmeyer, Chrom and Jacobson suggested that the cortical hormones of the suprarenal gland were concerned in the aetiology of psoriasis. This theory received support from the work of Incedayi and Ottenstein (1941) and Reiss (1949) and was accepted by Charpy (1949) and Barber (1950). Selye (1950) included it in the diseases of adaptation. Some success in treatment with adrenal cortical extracts had been claimed by Riehl (1936) and by Gruneberg (1937). With the advent of the adreno-cortical steroid hormones a real advance in therapy seemed possible. Early reports of oral and parenteral therapy were disappointing (Brodthagen *et al.*, 1951 ; Noguer More and Bassas Grau, 1952 ; and Ingram, 1954, with ACTH or cortisone, and Frank and Stritzler, 1955, with prednisolone). Some authors reported a temporary response during treatment usually followed by a severe relapse when this was discontinued (O'Leary, 1951 ; Falk, 1951 ; Hopkins *et. al.*, 1952 ; Coste *et al.*, 1953 ; Ferguson and Dewar, 1957). Local administration proved completely ineffective (Goldman *et al.*, 1952 ; Sulzberger *et al.*, 1953 ; Welsh and Ede, 1954 ; Portnoy, 1955), although a minority reported some success particularly in psoriasis of flexural distribution (Spies and Stone, 1950 ; Kalz *et al.*, 1955 ; Zelcer, 1954).

In 1957, a synthetic steroid, triamcinolone, became available, and a rapid response was reported in a proportion of cases treated orally (Shelley *et al.*, 1958 ; Kalz, 1958 ; Kanee, 1958). Topically it was ineffective (Shelley *et al.*, 1958 ; Robinson, 1958). Two further synthetic corticosteroids soon followed, methyl prednisolone and dexamethasone. It seemed important to decide whether one of these three new preparations showed significant advantage when administered orally in the treatment of psoriasis.

Design of Clinical Trial.

Cases were restricted to those with extensive lesions and it was decided to exclude the very young and those in whom toxic symptoms might be expected. Thus all patients with a history of peptic ulceration, mental instability or coronary artery disease, and those in whom glycosuria or gross hypertension were found on routine examination were excluded.

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Thirty patients satisfying the above criteria received one of the three steroids, triamcinolone, methyl prednisolone or dexamethasone. The sequence was determined by figures from random tables and the steroid administered in each case was known only to the hospital dispenser. The trial was blind as progress was recorded without knowing which steroid was involved.

Triamcinolone is practically equivalent to methyl prednisolone weight for weight in the treatment of rheumatoid arthritis (Hart *et al.*, 1958 ; Hicks, 1959). It may be a little more effective relatively in dermatological conditions (Rein *et al.*, 1957).

When this trial was planned, 1/6 or 1/7 by weight seemed to be a comparable dose of dexamethasone (Boland, 1958 ; Slater *et al.*, 1959). Recently however, it has been suggested that this is too low and that 1/5 or even 1/4 may more nearly represent the average conversion ratio (Hart, 1959). Using 0·5 mg. of dexamethasone or 4 mg. of triamcinolone or methyl prednisolone allowed the drugs to be given on a tablet-for-tablet basis which excluded a potential source of error in a blind trial.

The corticosteroids were administered thrice daily for one week, twice daily for two weeks and then once daily for three weeks. Progress was recorded at the end of the first, third and sixth weeks. All cases were treated with an ointment containing 3% salicylic acid and 4% prepared coal tar in an emulsified ointment base. No control group treated by local application alone was included owing to difficulty in obtaining sufficient patients with extensive lesions. However, half had been unsuccessfully treated with the same ointment for over three months immediately prior to this trial and a further five patients had used ½% dithranol ointment for a similar period without significant improvement.

Results.

The results are shown graphically in Fig. 1.

Side effects were few and mild, possibly due to the selection of cases. One patient complained of lassitude, another of depression and a third of heartburn with dexamethasone. A further patient who developed glycosuria was an obese woman aged 56 years who stated that her sister was overweight and diabetic and was being treated by diet alone. My patient's glycosuria disappeared when dexamethasone was discontinued. With methyl prednisolone, one patient complained of loss of appetite and another developed urticaria which was relieved by antihistamines and which cleared when methyl prednisolone was discontinued. Three patients experienced a feeling of well being. With triamcinolone, three patients reported hot flushes of the face.

Discussion

In the dosage employed, triamcinolone was the most effective oral steroid in the treatment of psoriasis and produced great improvement or complete remission in 60% of cases. This figure is in agreement with the findings of Shelley *et al.*

Rapid relapse in all patients when triamcinolone was discontinued is reported by the latter and some tendency to recurrence was noted by Kalz and Kanee. In the present series, of the six cases which cleared or greatly improved with triamcinolone, two remained clear for three months, and two for two months,

after which a gradual relapse took place, but their condition is still much better than before treatment was commenced. One case was practically clear six weeks after the trial ceased, and has not attended again. One patient gradually deteriorated after four weeks, but was controlled by a modified Goeckerman regimen. Thus four or possibly five of the six cases showed considerable remission and these figures bear comparison with established methods of treatment.

The comparable figures for methyl prednisolone and dexamethasone are small. With the former, out of four cases improvement was maintained for

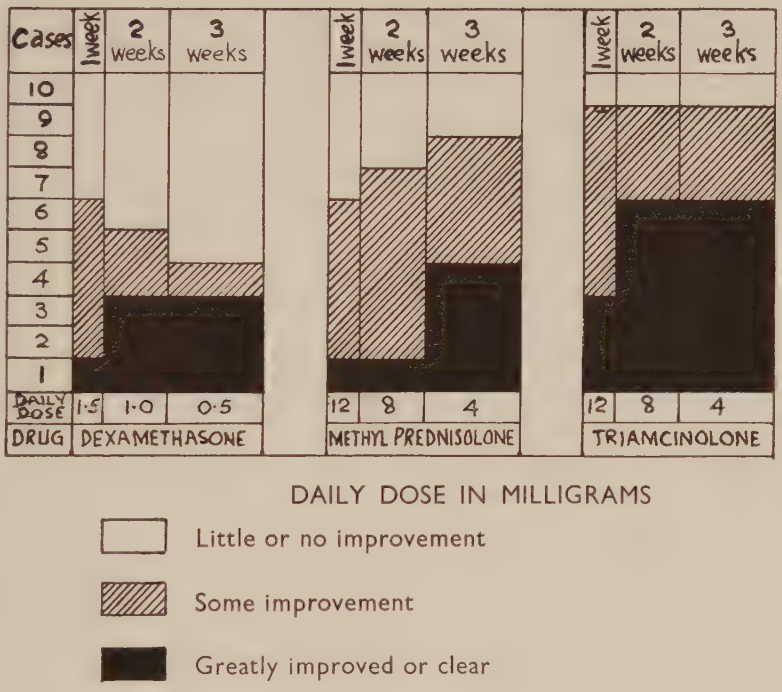

Fig. 1

three months in two and a third was still almost clear when last seen six weeks after completing the trial. Of three cases treated with dexamethasone, one relapsed within one month, one was still practially clear after six weeks and one did not attend again. It is possible that dexamethasone was not administered in a sufficiently high dose and this receives some confirmation from the downward trend of the graph in the cases showing only some improvement.

It must be emphasized that this paper is not intended to indicate the use of corticosteroids as a routine in psoriasis. They are powerful drugs with a considerable risk of side effects, and cannot be recommended for regular therapy in a chronic relapsing complaint. The cases in this trial all had extensive lesions, i.e. involvement of at least one-quarter of the skin.

The demonstration of a corticosteroid with a significant effect in psoriasis supports the idea of Ferguson and Dewar that a steroid may exist (or be elaborated) with a specific effect in this disease. Triamcinolone is worth consideration in attempting to relieve the distress of the psoriatic with extensive lesions.

Summary.

A comparison of the effects on psoriasis of oral administration of methyl prednisolone, dexamethasone and triamcinolone is described.

Triamcinolone proved the most effective in the dosage employed.

Although unsuitable for routine treatment, it produces remission in 60% of patients with extensive lesions, and in 50% this will last for some weeks.

I wish to thank Mr. R. Norman, M.P.S., Chief Pharmacist, Manchester and Salford Hospital for Skin Diseases for his assistance in this trial and Messrs. Merk, Sharp and Dohme who kindly supplied the dexamethasone (Decadron).

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INTRALESIONAL TRIAMCINOLONE ACETONIDE IN THE TREATMENT OF PSORIASIS.

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It is generally agreed that triamcinolone is more regularly effective in the treatment of psoriasis than either cortisone or prednisone (Calnan, 1960). The majority of psoriatic patients will improve on oral triamcinolone therapy (Shelley, Harun and Pillsbury, 1958), but the relapse rate after stopping the drug is considerable. The risks of such therapy are rarely justified except in extensive, hospitalized cases.

Local treatment with steroid preparations is of little use, although psoriasis may respond to ointments containing vitamin A and triamcinolone (Jarrett and Spearman, 1959). Obviously, injection therapy will only have a limited place in the treatment of psoriasis, but where indicated, it offers the advantages of oral steroid therapy without its hazards. It is of value in chronic resistant cases and in others with only a few lesions ; it may also be indicated cosmetically.

It has been known for some time that the local injection of hydrocortisone often reduces the psoriatic reaction (Goldman, O'Hara and Baskett, 1953). The injections, however, are often painful and the relapse rate is high, even over as short a period as one month.

Cohen and Baer (1960) used intralesional triamcinolone in order to decide whether the lesions would respond to oral therapy. Pelzig and Baer (1960) used triamcinolone acetonide 1% and triamcinolone diacetate 2·5% intralesionally in twenty patients. Nineteen were cleared or improved. Two relapsed within six months. James (1960) reported good results in 29 patients. One patient developed "temporary atrophy". The follow-up period was not stated. Gerard (1960) used injections of triamcinolone diacetate in varied strengths with good results. Solutions of from 2·5 to 25 mg. per ml. were used. All the treated lesions cleared for at least six months ; 16% relapsed over a period of eleven months.

The present report covers the use of triamcinolone acetonide (Squibb) in eleven cases. The initial supply contained 6 mg per ml. and was used subcutaneously in four cases.

Case Records.

Case 1.—A woman aged 45 had patches of chronic psoriasis on both elbows. On the first visit, half of one patch was infiltrated. After seven days the treated area appeared normal, apart from slight erythema. The other areas were then infiltrated and within a further fourteen days both elbows appeared normal.

Case 2.—A woman aged 42 was going on holiday to America and was desperate to lose three plaques of psoriasis on her leg, which had been present for three years. They cleared, following injection, within ten days.

Case 3.—A woman aged 37. In order to try its effect in acute cases, two areas were chosen from the many present in this patient and were injected. Although the untreated areas deteriorated, the injected areas cleared within ten days.

Case 4.—A youth aged 17 had an extensive plaque of many months' duration which involved most of the right arm. Injections were made at several points (1 ml. at each site) and islands of normal tissue approximately 5 cm. in diameter developed within fourteen days.

Subsequently a further supply of triamcinolone acetonide became available and an additional seven cases were treated in the same manner. This material was used at a strength of 5 mg. per ml.

Case 5.— A man aged 62 had had two large lesions on his back for twenty years. One half of one of the lesions was infiltrated. It cleared within ten days, apart from mild erythema which persisted for a further ten days.

Case 6.—A woman aged 28 had had several episodes of psoriasis. The present one had lasted twelve months and involved the scalp, the knees and the elbows. New lesions were appearing on the arms and legs. All the lesions on the left upper arm were injected. Two weeks later the treated area was clear, although the other areas had deteriorated.

Case 7.—A man aged 81 had had longstanding lesions on both elbows which cleared within ten days following injection. When seen ten weeks later, the injected areas were still clear, but fresh lesions had developed on the back and on one leg.

Case 8.—A girl aged 10 had widespread lesions which had remained unchanged for over twelve months. After seventeen days most of the lesions had improved, but the injected areas had cleared.

Case 9.—A girl aged 13 had had several lesions on both arms for seven years. The largest lesion was injected and it cleared in ten days. The other lesions remained unchanged.

Case 10.—A girl aged 15 had had several small lesions on both arms for five months. The main lesion on the right arm was chosen and half of it was injected : the treated area cleared within twelve days.

Case 11.—A man aged 43 had had large chronic patches on both shins and smaller lesions elsewhere for many years. A quadrant of a large lesion on the left shin was infiltrated and this area cleared. The remainder of the plaque showed some improvement, but the other untreated lesions were unchanged.

In all these cases the treated areas cleared in a maximum of seventeen days. A temporary erythema in the cleared areas persisted for up to fourteen days in some patients. None of the injected areas has become reinvolved even in those patients who have developed further lesions elsewhere. The follow-up period has varied from three to six months. The results are encouraging although the field of usefulness of this form of treatment is limited. A more extensive trial and follow-up is indicated as soon as further supplies of injectable triamcinolone acetonide become available.

Summary.

This is the first report of the use in Great Britain of triamcinolone acetonide by intralesional injection in the treatment of psoriasis. The results so far have been very encouraging.

I should like to thank Dr. G. W. Bamber, Dr. D. G. Freshwater and Dr. F. Glyn-Hughes for permission to study their patients; also Mr. W. W. Heseltine, of E. R. Squibb and Sons Ltd., Liverpool, for supplying the triamcinolone acetonide (Adcortyl-A Parenteral Squibb) and for secretarial help.

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HISTOCHEMICAL CHANGES IN PSORIASIS TREATED WITH TRIAMCINOLONE.

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This paper reports our histological findings in three psoriatic patients treated with systemic triamcinolone. We used this steroid as a research method to induce improvement in psoriatic patients without the need of local applications which might interfere with the histological examination of biopsy material. Triamcinolone was the first steroid able to induce worth while remissions in psoriasis and good results of its use have been reported (Shelley *et al.*, 1958). From clinical experience it seems probable that all psoriatics would improve if a sufficiently high dose were given. However, it is obviously undesirable to give large amounts of a potent steroid for a chronic and non-fatal condition. In addition, cases have been observed of generalized relapse following withdrawal after its use in moderately high dosage.

We decided to use triamcinolone in a dose of 4 mg. twice daily by mouth for the purposes of this experiment. Biopsies were performed at regular intervals to detect any histochemical changes occurring in the improving psoriatic plaques. A similar investigation was made by Braun-Falco (1959).

Investigation.

The first patient responded promptly and completely to this dose of triamcinolone, the second partially, and the third was uninfluenced. Biopsies were performed before and during treatment. Five specimens were taken from each of the first two cases and six from the resistant case. They were fixed in 70% alcohol and examined by the methods listed below.

Routine methods :

i. Haematoxylin and eosin.
ii. Ponceau.

Fluorescence techniques :

iii. Congo red and thioflavine T.
iv. Titan yellow : a specific method for demonstrating the granular layer.
v. Thioflavine T for nuclear protein.
vi. Thioflavine T following RNase digestion to demonstrate DNA.
vii. Thioflavine T following DNase digestion to demonstrate RNA.

All these techniques were described by Jarrett *et al.* (1959).

Histochemical methods :

viii. A modification of Baker's acid haematin method for phospholipids (Jarrett *et al.*, 1959).

ix. The method of Barrnett and Seligman (1952) for sulphydryl groups.

x. Gomori's (1950) technique for acid phosphatases.

xi. Best's carmine for glycogen.

In addition the thickness of the epidermis was measured by means of a micrometer eyepiece. Care was taken to ensure the epidermis had been cut at right angles (oblique cuts can be detected because islands of dermis appear in the artificially elongated rete pegs). Measurements were made on haematoxylin and eosin sections and were taken from the epidermal-keratin junction to the base of a rete peg. A simple arithmetical average was taken because during improvement the thinning of the epidermis was obvious and thus did not require statistical evaluation.

Case Histories.

Case 1.—A woman aged 37. She had suffered from psoriasis for many years. Just before she was given triamcinolone, she had an acute almost generalized relapse. The first biopsy specimen was taken from a spreading plaque on the left buttock ; triamcinolone was then given by mouth in a dose of 4 mg. b.d. A second biopsy was performed one week later on the same site. There had been a rapid response to treatment during this period, but the area subjected to biopsy was still clinically psoriatic. After a further 5 days' treatment, a third specimen was taken from the same site and by this time the skin in the biopsy area had become clinically almost free of psoriasis. Fourth and fifth biopsies were performed on the same region after 22 and 43 days' treatment respectively ; by this time all the psoriatic lesions had cleared.

Case 2.—A man aged 23. Widespread psoriasis for 6 years, with plaques on the body and scalp. A biopsy was performed on one of the chronic plaques on his left forearm and treatment with triamcinolone was commenced. A further biopsy specimen was taken from this site one week later ; clinically there had been no improvement. A third specimen was taken after a further week's treatment and a fourth after a total of 24 days of triamcinolone therapy, by which time there was a definite improvement in all lesions. A final biopsy was performed 10 days later when he was very much improved and the biopsy site had become clinically almost free of psoriasis.

Case 3.—A woman aged 65. Widespread psoriasis of four years' duration. There was no family history of the disease. The initial biopsy specimen was taken from the edge of a psoriatic plaque on her thigh. She was then given triamcinolone in a dose of 4 mg. b.d. Serial biopsies were performed on the same plaque 7, 14, 22, and 39 days after the commencement of treatment. All the biopsy material included some clinically normal skin. A final biopsy specimen was taken after 49 days' treatment from the skin of the thigh 15 cm. from the nearest psoriatic patch. No clinical improvement occurred and triamcinolone was gradually withdrawn.

Results.

Case 1.—The clinical response to triamcinolone was rapid and complete and was accompanied by histochemical and histological changes in the skin which are summarized in Table I. After one week's treatment, there was a reduction in the epidermal thickness, which after two weeks had been reduced by half. A granular layer was rapidly reformed and acid phosphatase activity was detected at the earliest phase of its establishment.

				ratin.							
2	8	Definite improvement	210	Early formation of granular layer. Parakeratosis patchy.	Keratin red-blue, epidermis thinner, nucleoli++	+	+	+++	±	++	++
3	13	Almost cleared	130	Granular layer well established. No parakeratosis.	Keratin nearly all red, nucleoli +	++	+	+++	+	±	−
4	22	Lesions cleared	110	Ditto	Keratin red-blue	++	+	++	+	±	±
5	43	,,	90	,,	Keratin mainly red	++	+	±	++	±	−

TABLE II.—*Summary of Histological Findings in Case 2.*

Biopsy.	Days of treatment.	Clinical state.	Thickness of epidermis (μ)	Haematoxylin and eosin.	Congo red, thioflavine T.	Titan yellow in granular layer.	Acid phosphatase in granular layer.	Cytoplasmic RNA.	DNA in upper epidermal cells.	Keratin	
										SH.	Phospholipids.
1	0	Widespread psoriasis	230	Typical psoriasis. Parakeratotic keratin.	Keratin blue, Nucleoli ++	−	−	+++	−	++	++
2	7	No change	230	Thick abnormal granular layer reformed. Patchy parakeratosis	Keratin red-blue, Nucleoli ++	Abnormal fluorescence of granular layer	+	+++	+	+±	+
3	15	Slight improvement	230	Reformed granular layer still abnormal. Patchy parakeratosis	Keratin blue, some areas red. Less normal than biopsy 2	Abnormal as in 2 above	+	+++	±	++	++
4	39	Definite improvement	170	Epidermis thinned. Granular layer well formed. Some parakeratosis	Keratin red-blue, Nucleoli++	+	+	+++	+	+	+
5	48	Almost cleared	130	Epidermis thinned. No parakeratosis	Keratin red, red-blue in patches, Nucleoli +	+	+	++	+	+	±

The fluorescence of the epidermal keratin with the congo red and thioflavine T technique changed from the blue of psoriatic keratin to the red of normal epidermal keratin during the first two weeks of treatment. The fluorescence remained normal until the final biopsy performed 43 days after the beginning of treatment. The abnormally high content of both sulphydryl groups and phospholipids in the psoriatic keratin was greatly reduced after two weeks' treatment and at the time of the final biopsy these had returned to the proportions which occur in normal epidermal keratin.

The desoxyribonucleic acid (DNA) content of the epidermal nuclei was examined by its fluorescence with thioflavine T after the ribonucleic acid (RNA) had been removed by digestion with ribonuclease. The DNA content of the epidermal cell nuclei in the upper part of the epidermis is very low in psoriatic skin ; in some cases only the basal cell nuclei fluoresce brightly. In the successive biopsy specimens there was a gradual return of nuclear fluorescence in the upper epidermis.

Cytoplasmic RNA was estimated by the intensity of the yellow fluorescence with thioflavine T after the DNA of the nuclei had been removed by desoxyribonuclease. The nucleoli still remained visible in the darkened nuclei because of their content of ribonucleic acid. Cytoplasmic RNA and the number of nucleoli are greatly increased in psoriatic epidermis (Fig. 1*a*). The biopsy performed after 13 days' treatment was from skin which was clinically almost normal ; it was also almost normal by the criteria of most of the histological and histochemical investigations. Nevertheless, the content of cytoplasmic RNA was abnormally high and the next biopsy specimen taken from clinically normal skin after 22 days' treatment was still abnormal. It was only after three weeks' further treatment with the same dose of triamcinolone that the cytoplasmic content of the RNA fell to approximately normal levels (Fig. 1*b*).

Case 2.—This patient responded very much more slowly than the first. The delay in clinical improvement was reflected in the slow alteration of the abnormal histological and histochemical features.

The thickness of the psoriatic epidermis slowly decreased but there was no reduction in epidermal thickness after the first two weeks' treatment. A thick, abnormal granular layer was reformed during the first six days and this had acid phosphatase activity. There was also some change towards normal of the colour fluorescence of the psoriatic keratin with the congo red and thioflavine T technique, but even after 48 days' treatment, this was not entirely normal (Table II).

The sulphydryl and phospholipid content of the epidermal keratin was reduced in the second biopsy specimen but had returned to pre-treatment levels by the time of the third biopsy taken eight days later. The fourth and fifth biopsy specimens showed reductions in both these components. The DNA of the nuclei of the upper epidermal cells showed some evidence of increasing to

normal levels in the second biopsy specimen but this trend was not maintained. It was not until the fourth and fifth biopsies that the nuclear DNA fluorescence had returned to the upper epidermal cells. The cytoplasmic RNA of the epidermal cells never fell to normal levels as in the first patient. There was some evidence of a reduced content after 48 days' treatment, but it was still above normal.

Case 3.—This patient completely failed to respond clinically to triamcinolone in a dose of 4 mg. b.d. She was treated for a total of 50 days. There were slight histochemical changes after 7 days' treatment, but these were not

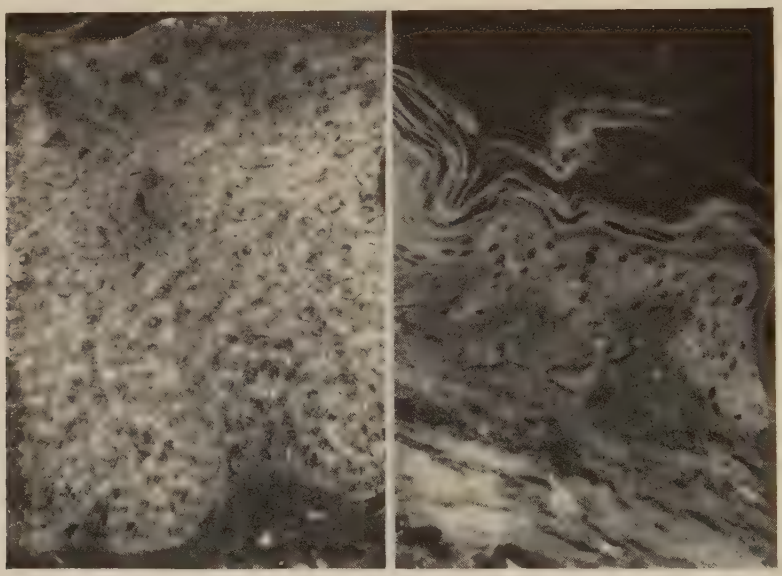

Fig. 1.

(*a*) Case 1 before treatment. (Fluorescence microscopy : fluorochromed with thioflavine T after digestion with DNase.) The nucleoli and cytoplasm fluoresce brightly because of their RNA content. The rest of the nuclei do not fluoresce because the DNA has been removed.

(*b*) Case 1 after 43 days' treatment. Same technique and same magnification as in (*a*). The epidermis is much thinner : no nucleoli are visible and the intensity of the fluorescence due to cytoplasmic RNA is much reduced.

maintained and a biopsy specimen taken two weeks later was essentially the same as before treatment was commenced.

After the first week there was some attempt to form a granular layer and this had acid phosphatase activity (Table III). In addition, there was some DNA in the nuclei of the upper epidermal cells. However, biopsy specimens taken after 14 and 22 days' treatment failed to reveal the re-establishment of a granular layer. It therefore appeared that the early tendency to form a

TABLE III.—*Summary of Histological Findings in Case* 3.

			PSORIATIC PLAQUE.							
Biopsy.	Days of treatment.	Clinical state.	Thickness of epidermis (μ).	Haematoxylin and eosin.	Congo red, thioflavine T.	Titan yellow.	Acid phosphatase in granular layer.	Cytoplasmic RNA.	DNA in upper epidermal cells.	Phospholipids in keratin.
1	0	Widespread psoriasis	350	Typical psoriasis. Parakeratosis	Keratin blue-green	−	−	+++	±	++
2	7	No change	450	Ditto	Ditto	Very early formation of granular layer ±	+	+++	+	++
3	14	,,	370	,,	,,	−	−	+++	−	++
4	22	,,	340	,,		−	−	+++	−	++

TABLE IV.—*Summary of Histological Changes in Clinically Normal Skin Adjacent to Lesions of Psoriasis in Case* 3.

			CLINICALLY NORMAL SKIN.							
Biopsy.	Days of treatment.	Thickness of epidermis (μ)	Haematoxylin and eosin.	Congo-red, thioflavine T.	Titan yellow granular layer.	Acid phosphatase in granular layer.	Cytoplasmic RNA.	DNA in upper epidermal cells.	Phospholipids in keratin.	Remarks.
1	0	150	Normal skin. No parakeratosis	Keratin red-mauve	+	±	+++	++	±	Normal skin adjacent to psoriatic plaque.
2	7	160	Ditto	,, ,, ,,	+	+	+++	++	±	Ditto
3	14	140	,,	,, blue-green	+	+	+++	±	+±	,,
4	22	65	,,	,, blue-yellow	+	+	+++	+	+±	,,
5	39	60	,,	,, blue-green	+	+	++	+	±	,,
6	49	50	,,	,, mainly red, some patches yellow	+	+	±	++	+	Taken at 15 cm. from nearest psoriatic lesion.

normal epidermis was not maintained during the subsequent weeks of treatment and no significant changes were detected after three weeks' therapy. Two further biopsies were performed on this patient, one after 39 and another after 49 days of triamcinolone therapy. During this time there had been no clinical improvement so it was not considered worth while to take further material from the psoriatic plaque. The first of these further specimens was of apparently normal skin adjacent to the plaque and the second of normal skin about 15 cm. from the nearest psoriatic lesion. These were compared with the normal skin which was removed with psoriatic skin in the four previous biopsies (Table IV) and with specimens of normal skin taken from the knee of three non-psoriatic subjects. The latter three specimens were subjected to the same techniques as those from the psoriatic patients. The results are shown in Table V. None showed parakeratotic keratinization, but the keratin layer was

TABLE V.—*Summary of Findings in Skin of Normal Knees.*

Biopsy.	Haematoxylin and eosin.	Congo red thioflavine T.	Cytoplasmic RNA	Nuclear DNA in upper epidermal cell nuclei.	Keratin	
					SH.	Phospholipids.
1	Keratin thick. Granular layer well formed. No parakeratosis	Keratin blue-green	+++	±	±	+
2	Ditto	Keratin red-mauve	±	+	−	−
3	,,	Keratin yellow-blue	+++	+	±	+

thicker than that of skin from other parts of the leg. The keratin of two of the specimens (1 and 3) gave an unusual fluorescence with the congo red and thioflavine T technique and in both there was increased phospholipid content compared with other epidermal keratin. The keratin of the skin of the knee of these two subjects therefore resembled psoriatic keratin more closely than normal epidermal keratin from other areas. It also closely resembled that of several of the biopsy specimens from apparently normal skin of the thigh of the patient who failed to respond to treatment (Case 3). In addition the epidermal cells of these two normal pieces of the skin of the knee had a very high content of RNA and thus resembled psoriatic epidermis. The other specimen (2) fluoresced more normally with the congo red and thioflavine T technique and the cytoplasmic RNA content was more like that of normal skin from other regions.

DISCUSSION.

Cytoplasmic RNA.—The first patient responded rapidly both clinically and histologically ; within two weeks all the histochemical findings had returned to normal with the exception of the cytoplasmic RNA of the epidermal cells.

This remained high until 43 days after the commencement of treatment, despite complete clearance of the lesions. The patient enjoyed a prolonged remission following the reduction of the dose of triamcinolone ; it was almost three months before lesions reappeared. The second case responded much more slowly and during the first two weeks there was little alteration in either the clinical or histological picture. It was only after 48 days' therapy that the psoriasis showed definite improvement. The cytoplasmic RNA never fell to normal levels and there was a rapid relapse when the dose of triamcinolone was reduced. The third patient failed to respond either clinically or histologically and the cytoplasmic RNA remained very high. It appears possible therefore that if this high content of cytoplasmic RNA, which is a manifestation of cellular activity, is not adequately reduced by steroid therapy, rapid relapse occurs when the drug is withdrawn. This may be an important point in the control of psoriatics with triamcinolone.

Epidermal thickness.—There was a marked reduction in the thickness of the epidermis in both the successfully treated patients. It is of interest that in the first case it fell much more rapidly and when it measured about 160 μ, there was definite clinical improvement. In the second, a much slower fall was recorded but again definite clinical improvement was noted at the time when the epidermal thickness had fallen to about this value.

Titan yellow.—As previously reported (Jarrett *et al.*, 1959) this fluorochrome induces a strong yellow fluorescence in the normal granular layer. This is therefore a very delicate method for the detection of the reformation of a granular layer. In addition, we have reason to believe that this fluorescence is dependent upon the presence of magnesium. If this is so, we have a clear indication of abnormal magnesium metabolism in psoriasis. This is of interest as magnesium is a catalyst in the oxidation of cysteine to cystine and it has been well established that the formation of cystine is defective in parakeratotic keratinization.

Nuclear DNA.—It was noted in psoriatic epidermis that there was a loss of nuclear fluorescence due to DNA in the upper epidermal cells situated immediately below the keratin layer. At times this deficiency extended down to the basal cells. In normal epidermis however, the nuclei immediately beneath the granular layer has a relatively high content of DNA. During the induced remissions in cases 1 and 2 there was a return towards the normal. These findings indicate that in psoriatic epidermis there is an alteration of the nuclear chromatin network in the upper epidermal cells. This rapidly returns to normal under the influence of successful triamcinolone therapy ; there is not the same time lag as with cytoplasmic RNA. The nature of this change in nuclear fluorescence has not been elucidated.

Phospholipids.—Previous workers (Snider *et al.*, 1949 ; Hollander *et al.*, 1954 ; Braun-Falco, 1958 ; Jarrett *et al.*, 1959) have reported an increased

phospholipid content in psoriatic keratin. During the remissions induced in the first two patients, there was a definite reduction of the phospholipid content of the keratin. This is thought to be due to the utilization of these compounds during normal keratinization. The energy derived from them is probably used for the polymerization of the polypeptide chains of the keratin molecule (Jarrett *et al.*, 1959). Proper utilization of phospholipids occurs after the formation of a granular layer and it is therefore most likely that the enzymes required for their breakdown are located in this region. The only active enzyme we have been able to detect in the latter is acid phosphatase, but in previous experiments we have not been able to remove the phospholipids by incubation with this enzyme (Jarrett *et al.*, 1959). These findings with psoriatic patients indicate that it is worth searching for the presence of other enzyme systems in the region of the granular layer.

Comparison between the Apparently Normal Thigh of Case 3 *and Skin from the Knees of Normal Non-psoriatic Subjects.*—The keratin overlying the apparently normal thigh skin of the patient who failed to respond fluoresced abnormally by the congo red thioflavine T technique on three occasions. Also all the biopsy specimens except one showed an abnormally high content of cytoplasmic RNA. The keratin of two of the specimens of normal knee skin also fluoresced abnormally, and both had a high cytoplasmic content of RNA. The keratin of the third specimen of knee skin gave the usual fluorescence with the congo red thioflavine T method and the epidermal cells contained a normal amount of RNA.

These findings suggest that the skin of the knee in certain normal non-psoriatic subjects has features that resemble those of psoriatic skin. The similarity between the normal skin of the knee and the skin in psoriasis is of interest as it indicates that epidermis from this site undergoes a different and more rapid type of keratinization than that in many other situations. The knees are one of the commonest places for the development of psoriasis and the reason may be that the type of keratinization in this area is half way towards psoriatic keratinization.

The histochemical abnormalities of the third patient indicate that there was a high degree of epidermal activity in her apparently normal skin and this could at least partly explain her failure to respond to the small dose of triamcinolone.

Summary.

Three cases of psoriasis were treated with triamcinolone in a dose of 4 mg. b.d. One responded rapidly, another had a partial remission and a third failed to respond.

Serial biopsies were taken from all the patients and these were studied by routine histological and histochemical techniques and by fluorescence microscopy. The results of these investigations are reported together with those in biopsy specimens of skin from the knees of three psoriatic patients.

A granular layer was rapidly reformed during a remission induced by triamcinolone, but in the epidermal cells the cytoplasmic content of RNA remained high even after complete clinical recovery. The significance of these findings is discussed.

We wish to thank Mrs. J. A. Hardy for her expert help in the preparation of the histological material.

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KERATOACANTHOMATA ASSOCIATED WITH PSORIASIS.

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Since the turn of the century there have been sporadic reports of crops of seborrhoeic keratoses following attacks of eczema (Radcliffe-Crocker, 1905) and it is common to see these lesions develop following extensive eczema and lichen planus. Acanthomata have been reported following eczema (Williams, 1956) and there have been isolated reports of multiple keratoacanthomata arising on areas affected by seborrhoeic dermatitis (Wilson, 1956) and a single lesion on a patch of chronic eczema (Lockwood, 1956).

The purpose of the present paper is to report a case in which multiple keratoacanthomata developed during an attack of psoriasis. It would appear that such a phenomenon has not been previously reported.

Case Report.

A Polish man, aged 37, who had been a labourer most of his life and had no contact with oil or tar, attended the department in 1952 with impetigo of the chin which responded to a local antibiotic. No other skin lesions were seen at that time. In April 1957 he attended again having had an itchy eruption on the limbs and trunk for four months which was found to be psoriasis. Treatment with Ung. Hydrarg. Ammon. et Picis Carbonis failed to resolve the eruption and on his second attendance a few weeks later he was given calciferol 50,000 units twice daily by mouth in addition. He was not seen again until November 1958, when he reported that the tablets had " cured " the eruption and he had not therefore attended the department again. He now reported an itching eruption on the trunk and limbs, present for about one month. This time the eruption was not classically psoriasiform, the lesions being orange in colour and some showed a little infiltration. It was thought that he might be suffering from parapsoriasis but the rash responded dramatically to the same local application used at his previous attendance and he ceased attending the department. He is adamant, however, that the rash cleared completely for a period of six months. In October 1959 he came back to the department with a generalized recurrence of typical psoriasis. He also had numerous scattered infiltrated and warty lesions on his trunk and upper limbs. Some of these lesions showed the characteristic morphology of a keratoacanthoma. Five such dome shaped lesions measuring approximately 1 cm. in diameter and showing a central keratinous plug are illustrated in Fig. 1. The largest lesion observed was situated on the left forearm and measured 4·5 cm. in diameter (Fig. 2a). A portion of this large ulcerated indurated plaque was taken for histological examination. Biopsy specimens were also obtained from smaller lesions at other sites. Treatment was instituted with ultra-violet light and tar baths, combined with Ung.

Hydrarg. Ammon. et Picis Carbonis, and the psoriasis responded rapidly. The infiltrated lesions also began to resolve. Fig. 2b shows the appearance two months later of the lesion depicted in Fig. 2a. When the patient was last seen in March 1960, all the infiltrated lesions had disappeared leaving slightly pitted white atrophic scars and his psoriasis was almost clear.

Histology.—Biopsy material obtained from this patient showed keratoacanthomata in various stages of development. An early stage of development of this tumour

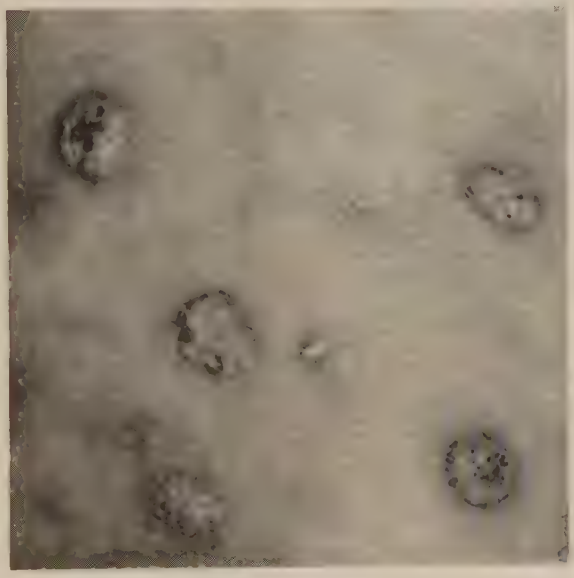
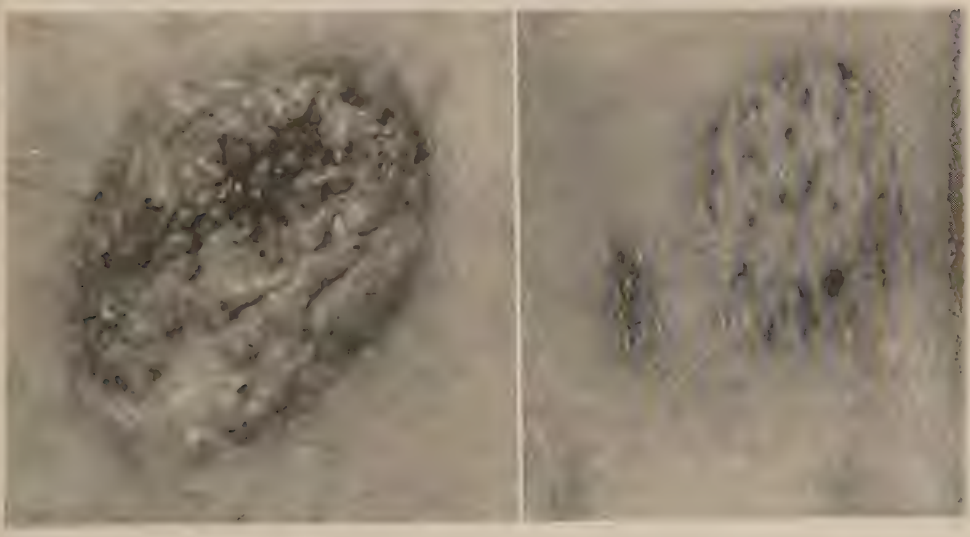


FIG. 1



(a) (b)

FIG. 2

showing hyperkeratosis and acanthosis of the hair follicle is illustrated in Fig. 3. This is similar to an early keratoacanthoma depicted in Fig. 5 of the paper by Calnan and Haber (1955).

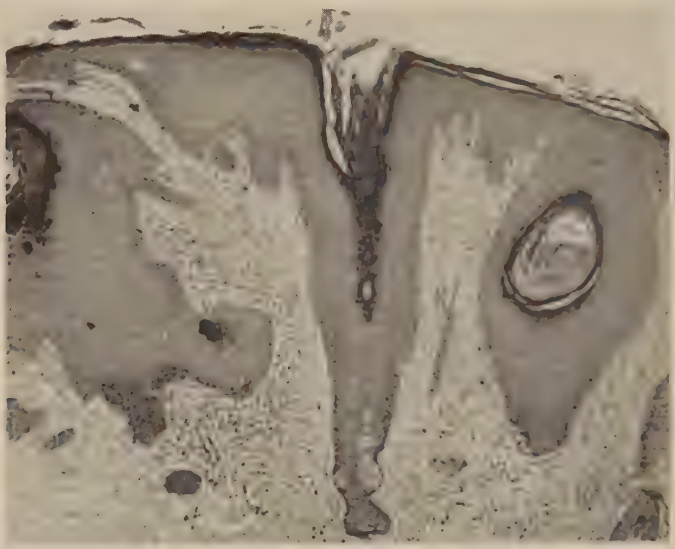


FIG. 3

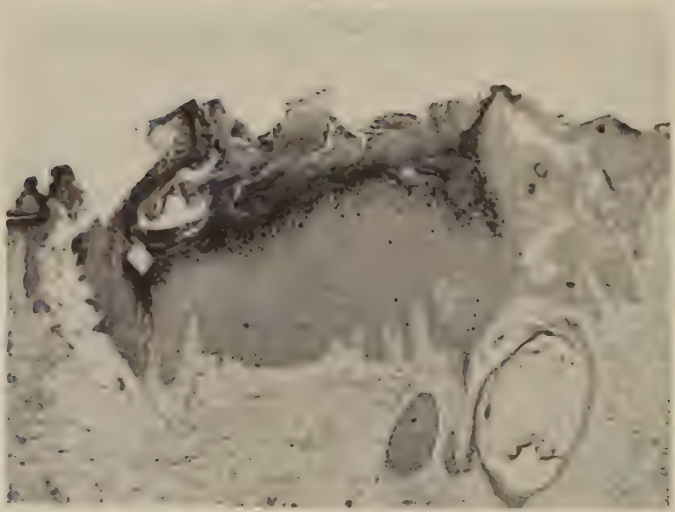


FIG. 4

A shallow saucer shaped keratoacanthoma similar to that reported by Ghadially (1958, 1959) as occurring naturally in man and in experimental animals painted with carcinogens was seen in our case also, and is illustrated in Fig. 4. The most interesting biopsy specimen, however, was the one obtained from the margin of the large ulcerated lesion shown in Fig. 2a. Here we observed large irregular columns and islands of

squamous epithelium infiltrating the corium (Fig. 5) and it was difficult to decide whether this was an unusually florid example of pseudocarcinomatous infiltration similar to that known to occur at the margin of some keratoacanthomata, or whether a true well differentiated squamous carcinoma had emerged. The marked round-cell infiltration of the corium, the singular absence of cellular and nuclear pleomorphism and the amount of keratin production observed in this lesion argued strongly in favour of the diagnosis of keratoacanthoma. On the other hand, the large size of the lesion and the extensive infiltration of the corium suggested that it might be a true carcinoma. The clinical course, however, has now shown conclusively that this was a keratoacanthoma.

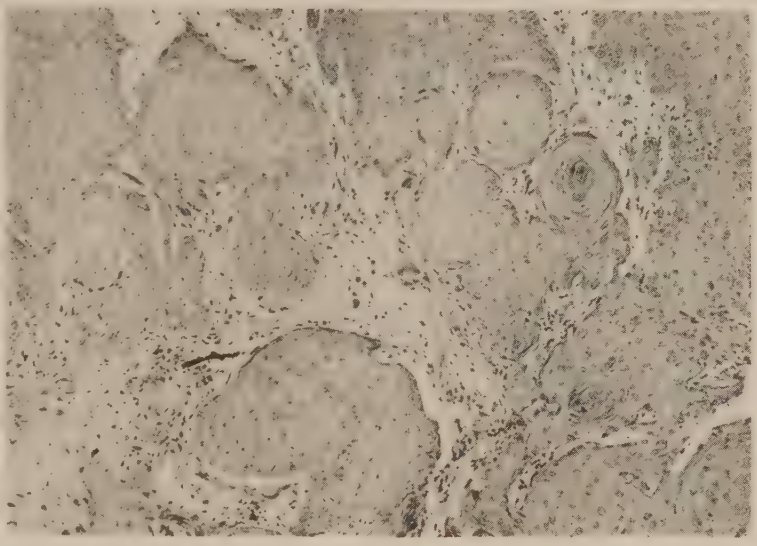


Fig. 5

Discussion.

The case presented in this paper shows that keratoacanthomata may develop following psoriasis and Williams (1956) found that acanthomata occurred after eczema. We have also observed patients in whom keratoacanthomata have arisen in pustules of rosacea or have followed simple mechanical trauma, such as a cut during shaving or a prick. Are such occurrences purely fortuitous or is there evidence here of a causal mechanism ? It can be argued that both psoriasis and keratoacanthomata are fairly common diseases and hence occasionally they are likely to be encountered simultaneously in the same individual. However, it must be realized that the occurrence of dozens of keratoacanthomata, as in the case reported, is in itself rare for as a rule patients with keratoacanthoma show only one or two lesions. Further, in our case we observed that the keratoacanthomata arose from psoriatic patches. If the association between these two conditions were fortuitous, the keratoacanthomata should have arisen indiscriminately in affected and normal skin. Similarly, in cases

of mechanical trauma, the fact that the tumour arises at the site of the injury and not elsewhere on the skin suggests a causal rather than a fortuitous relationship between the two.

Recent experimental work (Ghadially, 1958, 1959, 1960) has shown that tumours similar in morphology and behaviour to the keratoacanthomata of man are readily produced in various animal species by painting the skin with chemical carcinogens. Numerous workers (see Bullough, 1950) have also shown that animals' skin pretreated with one or more applications of a carcinogen and subjected to one of many apparently non-specific stimuli, such as mechanical trauma or chemical irritation, develops tumours. In fact it would appear that various agents capable of stimulating mitotic activity in minimally pretreated skin facilitate tumour production, while conversely agents which depress mitotic activity inhibit tumour production (Whiteley and Ghadially, 1952 ; Ghadially and Green, 1954 ; Ghadially, 1955). It is therefore conceivable that if human skin, rendered susceptible to tumour formation by genetic or carcinogenic factors, is subjected to trauma or becomes the site of diseases where epithelial cell proliferation occurs, tumours are likely to be produced. It is difficult to decide whether the therapeutic application of tar to this patient was a factor of aetiological significance. It can be argued that the amount applied was rather small (60 ml. of liquor picis carbonis in all) but it has been shown that in the mouse a minute amount of a potent carcinogen is sufficient to produce the essential neoplastic change (" initiation "), so that later on a non-specific stimulus can lead to tumour production. It is debatable whether such small doses would be sufficient in the case of man as it is known that not all tars are carcinogenic.

Summary.

A case of multiple keratoacanthomata developing during an attack of psoriasis is described and the significance of this association is discussed.

We are indebted to Dr. R. E. Church for advice and permission to report this case. This work was supported by grants from the University of Sheffield Medical Research Fund and the British Empire Cancer Campaign.

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CURRENT LITERATURE

SYSTEMATIZED DEPIGMENTATION AFTER RADIOTHERAPY OF MELANOMATA. K. H. Kärcher. (1960) *Dermatologica, Basel*, **120**, 255.

Stimulated by an account by Japanese authors of depigmentation spreading outwards from a melanoma, soon after radiotherapy, Kärcher records two cases of his own, which received large doses of fast electrons (at 15 MeV). Not only was there depigmentation of the irradiated sites, but extensive vitiligo-like patches developed on untreated parts of the body. The Japanese cases had had a nitrogen-mustard as well as the radiotherapy, and they could not exclude this as a possible factor, but Kärcher's cases had had nothing but radiotherapy. Incidentally, both his patients were alive and well, without sign of recurrence or metastasis, two and four years after treatment, respectively. J. F. S.

FURTHER RESEARCHES INTO THE PROLIFERATION-INHIBITING PROPERTIES OF A PHENANTHRENE DERIVATIVE ON THE SKIN. E. Läuppi and A. Studer. (1960) *Dermatologica, Basel*, **120**, 275.

A phenanthrene derivative, called Ro 2–7239, given intraperitoneally, inhibits the physiological proliferation of the epidermis of normal male rats. Furthermore, the preparation enhanced the castration-induced reduction of the process of nuclear division and the associated narrowing of layers, and antagonized mitotic activity and acanthosis induced by testosterone propionate, bilateral adrenalectomy, and hypervitaminosis A. This demonstrates that the preparation produces not only an antiandrogenic effect (as was supposed from earlier investigations), but has a broader spectrum of activity, which cannot yet be clearly defined.
(Slightly modified from Author's summary.) J. F. S.

BACTERIDS WITH FACIAL PREDILECTION. S. Irgang. (1960) *Dermatologica, Basel*, **120**, 286.

Two cases of bacterids with facial predilection are presented. The eruptions consisted of closely grouped lesions which had a tendency to form ringed plaques. Histologically, the lesions were vesico-pustules, and they all developed at the sub-epidermal level. Excision of a chronically infected gall-bladder in one case was followed by an apparent clinical cure. The other, while greatly improved one month after complete extraction of infected teeth, was not clinically cured fifteen months after surgical intervention. In this case, systemic therapy at different times with a sulphone, a sulphonamide, and antibiotic and a corticosteroid preparation did not prove fully effective. Opinions differ as to the value of eliminating septic foci in patients with bacterids.
(Author's summary.) J. F. S.

THE PERIARTERITIS GROUP AND THE SIGNIFICANCE OF GIANT-CELLS IN DISEASES OF THE VESSELS. W. Knoth and W. Meyhöfer. (1959) *Dermatologica, Basel*, **119**, 1.

In addition to classical periarteritis nodosa (Küssmaul and Maier, 1866), there have been described as separate entities a number of affections of the superficial arteries, and some have been grouped together as "giant-cell arteritides". The authors describe three cases of their own which illustrate the difficulty of putting cases into water-tight compartments, and in particular they assail the idea that the presence of giant-cells forms a basis for separation. They suggest that in one of their cases, in which the arteritic process had attacked vessels already showing the features associated with hypertension, the giant-cells were related to foci of destruction of the internal elastic lamina, while in a case of phlebitis saltans, cited for comparison, giant-cells were found in the thrombus, and had obviously been engaged actively in phagocytosis of red and white cells at the time of fixation. They seemed to be taking part in a re-canalization. In the arteritis they were probably phagocyting the disintegrating elastica, but this could not be established in the sections examined. This is an interesting discussion, with very extensive references. J. F. S.

EXPERIMENTAL AND CLINICAL INVESTIGATIONS WITH A NEW SULPHONAMIDE (MADRIBON). J. Künzle. (1960) *Dermatologica, Basel*, **120**, 83.

Sulphonamides, which had to yield their original high place in dermatological treatment to the antibiotics, have of late begun to recover some of their lost ground, as side-effects and bacterial resistance have increasingly diminished the efficacy of the latter. Madribon is 2,4-dimethoxy-6-sulphanilamido-1,3-diazine, and its *in vitro* spectrum is not dissimilar to that of sulphathiazole, but its clinical activity does not always run parallel to the *in vitro* sensitivity of the organism. Striking success was achieved in dysidrosis, suggesting that this eruption might be a bacterid. Some good results were obtained also in acne vulgaris and rosacea. The level of the sulphonamide in the blood cannot be used as a measure of its efficacy, and the possibility cannot be excluded that the drug has a special affinity for the skin. J. F. S.

THE HYPERTROPHIC FORM OF DARIER'S DISEASE. E. M. Elsbach and J. P. Nater. (1960) *Dermatologica, Basel*, **120**, 93.

It is curious that although Darier's pioneer description of the disease which is named after him mentioned hypertrophic lesions, this feature seems never to have been noted by subsequent writers. The authors here describe two cases in whom some of the lesions were of this type, with in places more complete disorganization of the follicles than has hitherto been recorded.
J. F. S.

ANALYSIS OF THE RESULTS OBTAINED IN ATOPIC DERMATITIS WITH OINTMENTS CONTAINING CORTICOSTEROIDS AND NEOMYCIN. M. K. Polano, R. De Vries and A. Delver. (1960) *Dermatologica, Basel*, **120**, 191.

Significantly better results were obtained from the combination of $\frac{1}{2}\%$ Prednisolone and neomycin than from hydrocortisone or prednisolone singly, or the petrolatum base. This was true even in cases showing no clinical evidence of infection, and may be due either to the fact that bacteria play a more important part in eczema than has hitherto been assigned to them, or else to a direct anti-eczema effect of neomycin. J. F. S.

HAILEY-HAILEY PEMPHIGUS IN GRANDFATHER AND GRANDSON. I. Gönczöl and L. Szodoray. (1960) *Dermatologica, Basel*, **120**, 214.

The clinical and histological features of these two cases are in line with the classical descriptions of this disease. The authors incline to the view that it is bullous morbus Darier. J. F. S.

THE EFFECT OF PROLONGED THERAPY OF ATOPIC DERMATITIS WITH TRIAMCINOLONE, DEXAMETHASONE AND 6-METHYL PREDNISOLONE. F. Kalz. (1960) *Dermatologica, Basel*, **120**, 65.

Sixty-eight patients with severe and long-standing atopic dermatitis have been treated with corticosteroids and observed for from 3 to over 20 months. Triamcinolone, 6-methyl prednisolone and detamethasone were used. Over 50% of the patients could be satisfactorily maintained with small doses (1 to 2 tablets a day). A considerable number of side-effects occurred, severe in 12 instances, but change of drug enabled treatment to be continued in all but two patients, who were intolerant of all three compounds used. Long-term management resulted in complete control in 12 cases, satisfactory control, with occasional relapses in 23, and improvement without complete control in 15 cases. The result was unsatisfactory in 3 patients, who did not respond to steroid therapy in the dosage used, and in the two patients intolerant of all these compounds. The relative merits and shortcomings of each of the preparations are discussed. J. F. .S.

EPIDEMICS OF TINEA CAPITIS DUE TO TRICHOPHYTON VERRUCOSUM CONTRACTED FROM CATTLE OR SHEEP. Z. Even-Paz and F. Raubitschek. (1960) *Dermatologica, Basel*, **120**, 74.

Trichophyton verrucosum is a common cause of animal ringworm and occasionally of human. Two small epidemics, involving eleven children, are here recorded from Israel. The dermatophyte had not previously been isolated in that country. The affected children lived in agricultural settlements in which cattle and/or sheep were infected with the same organism. After initial animal-to-human transmission, it is probable that further spread among the children was by direct or indirect human-to-human infection. The apparently healthy wool of some sheep could be pulled out easily and painlessly, and was found to be infected. J. F. S.

NEW PRINCIPLES AND MODES OF THERAPY OF ONYCHOMYCOSES. A. M. Arievich, O. G. Vikhreva, B. M. Lebedeva and Z. G. Stepanischeva. (1960) *Vestn. Derm. Vener.*, **5**, 30.

The authors refer to the recent sharp rise in the frequency of ringworm of the nails—due mainly to *Trichophyton rubrum*; from a pre-war 4–5% of dermatophytoses (favus and trichophytosis, principally of hands) to 85%, accounted for by *T. rubrum* infection of hands or feet (all toe nails affected in over 50% of patients).

In 14 patients with *T. rubrum* infection of nails, after scraping off the superficial or brilliant layers of the nail plate constant and repeated applications of keratolytic and fungicidal plasters were made to the nail and narrow margin of the immediately adjoining skin. This was relatively painless and did not irritate the adjoining skin. After removal of the nail, fungicidal plasters, e.g. 20% pyrogallic acid, were applied to the nail bed (6–8 times in 48 hours) for 48–96 hours. One photograph shows the removal with forceps of the macerated nail plate and horny mass of the nail bed after use of keratolytic plasters. Another shows two feet with all the nail plates removed. A third shows the crescent of new nail behind a blackened area due to impregnation of the nail bed with pyrogallic acid.

The treatment for the most part was ambulatory and lasted, on an average, 45–50 days. Growth of new nail began on the hands within 4–5, and on the feet, 5–6 weeks. Of 173 diseased nails 120 (77%) grew in healthy. Within a period of 3–7 months after the end of treatment, no relapse was noted in the skin of hands or feet treated by exfoliating methods (not described) and iodine ointment.

A detailed description is included of the preparation of various forms of keratolytic and fungicidal plasters, including: e.g. salicylic acid 50 G, benzoic acid 20 G to lead plaster 50 G. The plaster mass can be fixed in position with leucoplast and does not tend to spread as an ointment would do. No bandages are required.

The importance of all general hygienic measures, etc., is stressed. M. S. S.

RELATIVE FREQUENCY OF OCCURRENCE OF SEX CHROMATIN IN KERATOACANTHOMA AND SQUAMOUS CELL CARCINOMA. H. J. Heite and R. Rüssmann. (1960) *Derm. Wschr.*, **141**, 33.

A hundred skin biopsies of female patients suffering from common epithelial cutaneous tumours were examined as to the occurrence of cells containing sex chromatin. Staining was according to Feulgen's method. Only chromatin bodies of characteristic size, plano-convex shape and adherent to the cell membrane were considered. Similar frequency of occurrence (about 30%–35%) were found in 13 cases of basal cell epithelioma, 15 senile keratomata, 15 basal cell papillomata, 7 verrucae vulgares and 21 keratoacanthomata. Twenty sections of squamous cell carcinoma showed only a median frequency of 21·5%. It is considered that the difference is a significant one and may possibly be a help in the differential diagnosis between keratoacanthoma and squamous cell epithelioma. J. M.

SIMULTANEOUS OCCURRENCE OF SCHAMBERG'S CONDITION, ANNULAR PURPURA AND A COAGULATION ANOMALY. A. Leovey and K. Vezekenyi. (1960) *Derm. Wschr.*, **141**, 37.

Two patients suffering from Schamberg's disease are described, one of which showed also evidence of annular purpura and hypo-fibrinogenaemia, whilst the other also had a tendency to haemophilia.

The various haemorrhagic and pigmentary dermatoses are considered to be manifestations of the same pathology and the importance of diffuse changes in the capillaries is stressed.

The pathogenesis of the transient coagulation anomaly as well as a possible connection with Schamberg's disease remain obscure. J. M.

SUPERFICIAL THERAPY OF DERMATOSES WITH FAST ELECTRONS OF STRONTIUM 90/YTTRIUM 90. R. Anger. (1960) *Derm. Wschr.*, **141**, 115.

"Dermaplatten Büchler" emitting β rays of the above description were used. The physical qualities of the rays, the dosimetric details and technique are discussed. During the last 3 years 61 "flat" cavernous haemangiomata in children and 101 "flat" or slightly elevated cutaneous epitheliomata (basal and squamous cell as well as a few intraepidermal lesions) were treated with gratifying results. Some carcinomata had only a single treatment. J. M.

TREATMENT OF ECZEMA WITH CHLORINATED PREDNISONE ACETATE. R. Ledig. (1960) *Derm. Wschr.*, **141**, 121.

Nearly 250 patients were treated with an ointment containing 0·1% 6 α chlorinated prednisone acetate and 0·5% neomycin. Nearly 90% of the cases responded; 4·4% were intolerant to the base. J. M.

4,4′-DIOXYDIPHENYL AS CAUSE OF CONTACT ECZEMA DUE TO DRESS PERSERVERS. K. H. Schulz and W. P. Herrmann. (1960) *Derm. Wschr.*, **141**, 124.

Twelve cases are described. The preservative D.O.D. provoked strongly positive reactions in all cases but in 6 patients there were also positive patch test results to accelerators etc. D.O.D. was also the allergen responsible in cases of contact dermatitis due to rubber condoms. J. M.

IMMUNOLOGICAL STUDIES ON PROPERDIN AND SPECIFIC ANTIBODIES AGAINST DEEP MYCOSES. T. H. Sternberg and E. G. McNall. (1960) *Derm. Wschr.*, **141**, 138.

Properdin is a serum globulin of importance for natural immunity and exerts an inhibitory effect on viruses and microbes. Evaluation of properdin content is based on this inhibitory property. More specific estimation of the properdin content are based on the selective inactivation of a component of complement in the presence of either inulin or zymosan. The natural immunity against deep mycoses depends on species, race, age and on physiological circumstances. The serum properdin value can be lowered through repeated injections of highly concentrated inulin over several weeks. Experimental animals whose properdin has been thus diminished are more susceptible to develop deep mycoses than the controls. Animals who were treated with lower concentrations of inulin and whose properdin values rise after temporary fall above the controls showed significantly higher resistance against mycoses. J. M.

BUTAZOLIDINE TREATMENT OF THROMBOPHLEBITIS. M. Hornemann. (1960) *Derm. Wschr.*, **141**, 358.

Three hundred and ten cases of mostly severe and extensive superficial thrombophlebitis were treated by intramuscular injection. One ampoule daily for three consecutive days was given and the course was repeated after 5 days. Average duration of treatment was 12·7 days. Results are superior to anticoagulants and subjective as well as objective improvement was quick to follow. There is no need for prolonged rest and there were no toxic side effects. J. M.

DRUG ERUPTION PRESENTING AS ARTERIOLITIS ALLERGICA CUTIS IN A PATIENT SUFFERING FROM ADVANCED ARTERIOSCLEROSIS. H. Gertler. (1960) *Derm. Wschr.*, **141**, 370.

The rash was classified as the haemorrhagic type of Ruiter and seems to have been provoked by tablets containing a pyrazolone derivate. The 66-year-old male patient died. J. M.

CONTACT DERMATITIS DUE TO HYDRAZIN SULPHATE. B. Brandt. (1960) *Derm. Wschr.*, **141**, 376.

Hydrazin is being used increasingly in the pharmaceutical industry to produce insecticides, fungicides, developers, as reducing agent in metallurgy, in the production of anticorrosive substances and even in the manufacture of propelling agents for rockets. Hydrazin causes irritation of the respiratory and ocular mucous membranes as well as contact dermatitis. Five cases are described which occurred in a chemical plant. Patch tests to 2% aqueous solution of hydrazin were uniformly positive, whilst 13 controls showed negative results. J. M.

THE ROLE OF HISTAMINE AND HISTAMINE-LIKE SUBSTANCES IN THE CAUSATION OF ABNORMAL PERMEABILITY OF CUTANEOUS VESSELS AS FAR AS THE PRODUCTION OF BULLAE IS CONCERNED. O. K. Schaposchnikow. (1959) *Derm. Wschr.*, **141**, 381.

The author does not come to any definite conclusion regarding the mechanism of the cutaneous reaction in bullous dermatoses. It is even more difficult to decide whether the changes of vascular permeability in these cases are caused by histamine-like substances produced after cutaneous damage. Maybe a neurogenic process could be responsible which is being transmitted not unlike an axon reflex. It is likely that the direct noxious action of histamine-like substances on the vessel wall is an important factor in the pathogenesis of abnormal permeability in bullous eruptions. J. M.